REMARKS

Claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95 are currently pending. Applicants have amended claims 1 and 53 to recite "wherein the amount of edetic acid or an edetic acid salt results in a reduction in the incidence of spray anomalies." Support for this amendment is found in the specification on page 3, line 19 to page 4, line 1. No new matter has been added.

(a) Claims 1-14, 16, 18-20, 22-31, 38-66 and 70-93 are not obvious over Freund *et al.* (DE 19653969 as evidenced by US 2001/0008632) under 35 U.S.C. § 103

Claims 1-14, 16, 18-20, 22-31, 38-66 and 70-93 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Freund *et al.* (DE 19653969 as evidenced by US 2001/0008632). Applicants point out that US 2001/0008632, which claims priority to WO 98/27959 or PCT/EP97/07062, is now abandoned and US 2007/077207, which is a continuation of US 2001/0008632, has granted as US Patent 7,470,422. Furthermore, to the extent this rejection might still be applied to the claims as presently amended in this application, applicants respectfully traverse.

Freund *et al.* cannot form the basis for an obviousness rejection because it teaches away from the presently claimed invention in two main aspects. According to MPEP 2144.05 (III), a *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *See, In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997). First, Freund *et al.* teaches the use of a minimum concentration of an edetic acid salt of 50 mg/100 mL, pH 3.4, in order to reduce the incidence of spray anomalies (see Table 1 of Freund *et al.*, a concentration of $\geq$ 50 mg/100 mL of EDTA, pH 3.4, in an *ipratropium bromide* solution yielded "0" spray anomalies as compared to tests run at lower levels of EDTA). Freud *et al.* also recites in the specification that a preferred range of the quantity of complexing agent is between 25 and 75 mg/100 mL solution, especially between 25 and 50 mg/100 mL (see page 1, ¶ 13). On the other hand, the present invention (1) teaches that significantly less than 50 mg/100 mL of edetic acid salt is needed to demonstrate a reduction in the scattering of the composition delivered (see specification on page 3, line 28, to page 4, line 1) and (2) has a claim limitation of a complexing agent comprising edetic acid or an edetic acid salt in an amount of greater than 0 and up to 25 mg/100 mL (see specification on page 6, line 27, to page 7, line 2). Second, Freund *et al.* teaches a pH range of 3.2-3.4. As stated in the current specification, the reduction of the

amount of edetic acid or edetic acid salt in the formulation allows the pH to be lowered, which results in the advantage of long-term stability of the formulation (see page 4, lines 4-7). In the presently claimed invention, the pH between 2 and 3 is not taught by Freund *et al.* For these reasons alone, Freund *et al.* cannot form the basis for an obviousness rejection.

The Office, however, states that Freund *et al.* recites a larger range of Na-EDTA of between 10 and 100 mg/100 mL. According to MPEP 2144.05(III), applicants can overcome a *prima facie* case of obviousness based on overlapping ranges by showing the criticality and unexpected results of the claimed range. Applicants have provided data to demonstrate these results (see previous reply to Office Action and data re-presented herein, see Attachment). The Examiner argues that this data was not persuasive because Table 1 of Freund *et al.* shows 8 tests performed on formulations containing 1, 0.1, 1, 50 and 75 mg/100 mL EDTA but that these data did not contain 10 mg and 25 mg amounts as shown in the data provided by applicants. As an initial matter, applicants point out that the data provided relates to tiotropium bromide solutions, whereas Table 1 of Freund *et al.* relates to *ipratropium* bromide. If applicants were to observe the trend in Table 1 of Freund *et al.*, it might be expected that a tiotropium bromide solution at pH 3.2 containing 50 mg/100g of EDTA would show no devices with spray anomalies. However, the data presented herein at pH 3.2 shows the largest number spray anomalies at 50 mg/100g NaEDTA. More importantly though, the unexpected results of the present application relate to the least amount of spray anomalies for tiotropium bromide solutions found at *low* levels of EDTA and *low* pH levels ($pH \leq 3.0$). This was not taught or could be deduced by the teachings of Freund *et al.*

For all of the above reasons, applicants request reconsideration and withdrawal of this rejection.

(b) Claims 1-14, 16, 18-20, 22-31, 38-66 and 70-93 are not obvious over Jager *et al.* (WO 9413262) in view of Bozung *et al.* (DE 19921693 as evidenced by US Patent 6,433,027) under 35 U.S.C. § 103

Claims 1-14, 16, 18-20, 22-31, 38-66 and 70-93 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Jager *et al.* (WO 9413262) in view of Bozung *et al.* (DE 19921693 as evidenced by US Patent 6,433,027). Applicants respectfully traverse.

Jager *et al.* cannot form the basis for an obviousness rejection because it teaches away from the presently claimed invention. For example, Jager *et al.* is directed to pharmaceutical solutions containing hydrofluorocarbon (HFC) propellants, whereas the presently claimed

invention is directed to specific *propellant-free* inhalable formulations. In Jager *et al.*, the preferred propellants used are HFA 227 and HFA 134a. One of skill in the art would not look to propellant-containing formulations for guidance in preparing *propellant-free* formulations. Moreover, Jager *et al.* does not exemplify a formulation comprising tiotropium bromide, a solvent and an acid, where the formulation has a pH range of 2.0-3.0 and spray anomalies are reduced with low levels of edetic acid or edetic acid salt.

Bozung *et al.*, on the other hand, does not disclose or teach the invention as recited in pending claims, specifically with regard to the stability of tiotropium salts in the pH range of 2.0-3.0 and reduction of spray anomalies with low levels of edetic acid or edetic acid salt. In fact, Bozung *et al.* teaches in one instance (see Table on column 7, lines 20-31) that the pH of its formulation is at a pH of about 3.4. Moreover, Bozung *et al.* is silent with respect to the specific dependence of tiotropium salt stability on pH and provides no motivation to leave the disclosed pH range of about 3.4. In contrast, the present claims teach that the pharmaceutical preparation of a tiotropium salt has a preferred lower pH limit of 2.0 and an upper pH limit of 3.0.

Additionally, the combined teachings of Jager *et al.* and Bozung *et al.* do not form the basis for an obvious rejection because Jager *et al.* is not art relevant to the presently claimed invention (propellant versus *propellant-free* solutions) and Bozung *et al.* are missing key elements of the claimed invention – edetic acid concentration and its affects on spray anomalies and pH (stability).

Based on the claim amendments and arguments made herein, applicants request reconsideration and withdrawal of this rejection.

(c) Claims 38-49, 51-52, 81-92, 94 and 95 are not obvious over Freund *et al.* or alternatively over Jager *et al.* in view of Bozung *et al.* as applied to claims listed above, and further in view of Weston *et al.* (WO 9114468) under 35 U.S.C. § 103

Claims 38-49, 51-52, 81-92, 94 and 95 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Freund *et al.* or alternatively over Jager *et al.* in view of Bozung *et al.* as applied to claims listed above, and further in view of Weston *et al.* (WO 9114468). Applicants respectfully traverse.

As discussed above, Freund *et al.* does not teach or suggest the elements of the presently claimed invention. Likewise, Bozung *et al.* teaches a pH of about 3.4, which by analogy to the arguments made above with Freund *et al.*, cannot teach the low pH of the

presently claimed invention and the reduction of spray anomalies with low levels of edetic acid or edetic acid salt. Although Weston *et al.* relates to inhalation devices, it is not enough to overcome the defects (or lack of teachings) of Freund *et al.* and Bozung *et al.* in forming the basis for an obviousness rejection of the presently claimed invention.

The combination of of Jager *et al.* and Bozung *et al.*, as argued in (b) above, are not a proper basis for an obviousness rejection. In turn, the addition of Weston *et al.* does cure these defects and thus, the combination of the three references does not form the basis for obviousness rejection of the presently claimed invention.

For all of the above reasons, applicants request reconsideration and withdrawal of this rejection.

(d) Rejection of claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95 for Obviousness-type Double Patenting should be withdrawn

Claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of co-pending applications:

(1) 11/068,134 (US 20050147564);

(2) 10/392,558 (US 20040019073);

(3) 11/267,354 (US 20060057074, now abandoned, 12/201,149, filed 8-29-08 is currently pending); and

(4) 11/006,940 (US 20050148562).

According to MPEP 804(I)(B)(1), "if a provisional nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer."

All of the above-listed copending applications were filed after the earliest effective filing date of the present application and qualify as "later-filed" applications. Furthermore, the double patenting rejections are the only remaining rejections in this application. Thus, according to the MPEP provision above, terminal disclaimers are not necessary for allowance

of the present claims. Applicants believe that the double-patenting rejections are rendered moot and withdrawal of the same is respectfully requested.

In view of the above remarks, applicants respectfully submit that this application is now in condition for allowance and earnestly request such action.

If any points remain at issue which can best be resolved by way of a telephonic or personal interview, the Examiner is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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ATTACHMENT: Experimental findings concerning spray quality of formulations

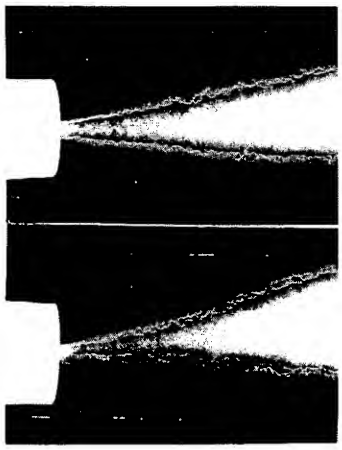
I. Composition of the investigated solutions:

Tiotropium	NaEDTA	BACl	Purified water ad	pH value
0.099 mg	50 mg	10 mg	100 g	2.7
				3.0
				3.1
				3.2
	25 mg			2.7
				2.8
				3.0
				3.1
				3.2
	10 mg			2.7
				2.8
				3.0
				3.1
				3.2
	0 mg			2.7
				3.3

The dosage 0.099mg relates to tiotropium. 1 mg tiotropium corresponds to 1.2495 mg tiotropium bromide;

"BACl" is Benzalkonium chloride;

II. Determination of spray quality:
For assessment of the spray quality the devices were sprayed under a cold light lamp over black paper into a vent. The evaluation was performed visually. The following picture describes a spray generated normally:



III. Results:

The following table gives an overview of actuations that were to be classified as sprays with deviations from the typical spray pattern in dependency from the chosen formulation:

pH value	NaEDTA [mg/100g]	Sprays with deviation			
		Devices		Actuations	
		No. of devices having spray deviation / total no. of devices tested	% of devices having spray deviation	No. of actuations having spray deviation / total no. actuations	% of actuations having spray deviations
2.7	0	0/40	0 %	0/15600	0 %
	10	0/40	0 %	0/15600	0 %
	25	1/40	2.6 %	1/15600	0.01 %
	50	28/40	70.0 %	2667/15600	17.10 %
2.8	10	0/40	0 %	0/15600	0 %
	25	2/40	5.0 %	11/15600	0.07 %
3.0	10	1/40	2.5 %	1/15600	0.01 %
	25	0/40	0 %	0/15600	0 %
	50	5/40	12.5%	13/15600	0.08 %
3.1	10	1/40	2.5 %	1/15600	0.01 %
	25	1/40	2.5 %	1/15600	0.01 %
	50	2/40	5.0 %	2/15600	0.01 %
3.2	10	0/40	0 %	0/15600	0 %
	25	1/40	2.5 %	1/15600	0.01 %
	50	2/40	5.0 %	3/15600	0.02 %
3.3	0	0/40	0 %	0/15600	0 %

An improvement of spray quality at lower pH values (pH 2.7-3.0) in combination with lower NaEDTA concentrations (10 and 25 mg) is observed. Formulations with 10 and 25 mg Na EDTA in pH range of 2.7 to 3.2 show not more than 0.1% of all actuations to be classified as sprays with deviations from the typical spray pattern.